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10/522,650	01/22/2005	Oleg Iliich Epshtein	841/6	7546

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GIBSON & DERNIER L.L.P.
900 ROUTE 9 NORTH
SUITE 504
WOODBRIDGE, NJ 07095

EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,650	EPSHTEIN ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *3 and 4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/18/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received January 9, 2008 are acknowledged.

Claims 1 and 2 have been amended.
Claims 5-7 have been added.
Claims 1-7 are pending in the instant application.
Claims 3 and 4 stand withdrawn from consideration as being drawn to a nonelected invention. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the restriction requirement mailed February 21, 2007.

Claims 1, 2, and 5-7 are under examination in the instant office action.

The declaration of inventor Oleg I. Epshtein under 37 CFR 1.132 received January 9, 2008 is acknowledged and will be discussed with the rejections of record to which it is addressed.

Information Disclosure Statement

2. The IDS form submitted 3/18/08 is acknowledged. It is noted that many of the references are in Russian and that no English language translation has been provided. These are SU 1331508, SU 1730144, RU 96113138, the Register of Pharmaceuticals in Russia, and Vyazov, O.L. These references have not been considered in their entirety and have only been considered as to their extremely limited description in the instant specification. It should be noted that a complete translation of the aforementioned documents may indicate that these references are applicable prior art under one or more statutes.

Specification

3. Applicant's amendment to paragraph 12 of the instant specification is objected to in that there is no paragraph in the instant specification identified as [0012]. It is suggested that the location of the paragraph in question be identified by page number using the pagination of the specification as filed. Note that amendments are made to the specification as filed, not to the formatting arrangement that appears in any pre-grant publication of the instant application. Further, the submitted replacement paragraph still does not comply with the Sequence Rules found in 37 CFR 1.821-1.825. Specifically, the disclosed amino acid sequence is not identified by a SEQ ID number in the text of the specification. Appropriate amendment is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1 and 2 under 35 U.S.C. 112, second paragraph, as being indefinite has been withdrawn in view of applicant's claim amendments received January 9, 2008.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order

for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1 and 2 stand rejected and newly presented claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Salerno (US patent 6,150,500, of record) in view of Davenas et al., Epshtein et al., and Feldman et al. (US Patent 5,741,488) for the reasons of record.

The office action mailed July 9, 2007 states:

> Salerno teaches antibodies to endothelial nitric oxide synthase (eNOS) and their methods of production (see entire document, particularly the abstract and column 11). These antibodies are taught as being present in compositions for use in methods of treatment (see particularly columns 13 and 14).
>
> These teachings differ from the instant claimed invention in that the antibodies in the compositions of Salerno are not disclosed as having been made by multiple consecutive dilutions and exposure to external factors.
>
> Davenas et al. teach very low concentrations (i.e. ultra low) of anti-IgE antibodies produced by repeated serial dilutions and exposure to the external factor of mixing by using a vortex (see entire document, particularly page 816 and the legend of Fig. 1). These antibodies maintain their ability to induce a physiological response, measured by the basophil degranulation, even at such low concentrations (see particularly the abstract, figure 1, and Tables 1-3).
>
> Epshtein et al. teach that potentiated antiserum when administered in very low doses causes measurable biological responses in vivo (see entire document, particularly the abstract).
>
> Feldman et al. teach that antibody based therapies are expensive and that lower doses of antibodies offer the advantage of lower financial costs to the patient (see entire document, particularly lines 20-25 of column 3).
>
> Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make compositions comprising very low doses of anti-eNOS antibodies. Motivation to do so comes from the teachings of Salerno that his anti-eNOS antibodies are to be used for methods of treatment, the teachings of Feldman et al. that low doses of antibody result in lower financial costs to patients, and the teachings of Davenas et al. and Epshtein et al. that very low doses of antibody maintain biological activity. As such, the skilled artisan would be able to make a biologically effective medicament that would impose less financial costs on patients. A person of ordinary skill in the art would have a reasonable expectation of success in making and using such compositions based upon the two distinct model systems of Davenas et al. and Epshtein et al., both of which disclose that antibody solutions maintain biological activity even when highly diluted.
>
> Further, the courts have held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). See MPEP § 2144.05. Note that in the instant situation, the general conditions are disclosed by Salerno and identifying optimum or workable ranges for dilutions of the antibodies disclosed by Salerno requires only routine skill in the art.

Applicant's arguments filed January 9, 2008 have been fully considered but they are not persuasive. Applicant begins by arguing that an NIH report and the declaration of inventor Epshtein indicate that homeopathic dilutions of antibodies are efficacious.

This argument has been considered but is not material to the question of obviousness since the efficacy of diluted antibody solutions is not an issue raised in the rejection of record.

Applicant's next argument is that the antibodies disclosed in the primary reference of Salerno et al. *bind* NO synthase, whereas the antibodies of the instant claims compositions *do not bind* NO synthase.

This argument is not persuasive. The limitation of "not binding" is absent from claims 6 and 7, and thus applicant is arguing limitations not claimed. In claims that do recite the non-binding limitation, the argument is still not persuasive. As applicant has repeatedly asserted and as is restated on pages 5-7 of the 1/9/08 response, "Homeopathic dilutions and homeopathic technology have been known in the field of homeopathy in the US to anyone of average skill in that field for almost 200 years, as written in the referenced NIH report." Neither the instant claims nor the instant specification indicate that any additional method steps or techniques are performed as part of "potentiation" that turn an antigen binding antibody into one that no longer binds its target antigen. As such, by performing the routine and well known techniques of homeopathy disclosed in the rejection of record a person of ordinary skill in the art would arrive at the instant claimed invention since the same procedures are used in their manufacture. Alternatively, if applicant is arguing that the recited composition does not bind the target antigen because the antibodies have been diluted to the point that no antibody molecules remain present in solution, the rejection of record provides for this as well since dilution ranges overlapping with those of the instant claims are disclosed.

Applicant further argues that the declaration of inventor Epshtein provides data to support the secondary consideration of commercial success, and that therefore the rejection should be withdrawn.

The argument of commercial success is not persuasive. First, evidence of commercial success must be commensurate in scope with the claims. The declaration discusses the efficacy of orally administered tablets comprising specified homeopathic dilutions of antibodies to NO synthase. The source and epitope specificity of the antibodies (other than that they are e-NOS antibodies and therefore reasonably bind the

antigen e-NOS) is not given in the declaration. The instant claimed products encompass one or more generic homeopathic dilutions of NO synthase antibodies and thus are not commensurate in scope with the declaration. As such, the specific dilutions and tablet form disclosed in the declaration does not support the claimed genus of compositions. Second, to be persuasive an argument of commercial success must show explicit sales results that demonstrate evidence of market share, including such things as total sales for competing products in the market, the differences between these competing products and applicant's product, total sales for products embodying the invention, pricing of the various products, information on advertising within relevant markets and any other information relevant to the inquiry. In other words, applicant must establish a nexus between the claimed features and the commercial success. As such, commercial success, if it exists, cannot be derived from other factors such as heavy promotion, advertising or brand name recognition. Note that gross sales figures do not show commercial success absent evidence as to market share. See *Cable Electric Products, Inc. v. Genmark, Inc.* 770 F.2d 1025, 226 USPQ 881 (Fed. Cir. 1985). In the instant declaration, inventor Epshtein discloses that:

> *"The medicament as claimed in the referenced application is now available as an over the counter (OTC) medicament in Russian and several foreign countries. The sales of the claimed medicament have propelled it to one of the top 20 OTC medicaments with about 10 million items manufactured and sold." (page 5 of the declaration)*

However, this data is irrelevant since the OTC market encompasses medicaments for all sorts of unrelated diseases and disorders, including such things as aspirin for headaches. What is needed is a comparison to other medicaments used to treat erectile dysfunction. Further, while the declaration states that 10 million items have been manufactured and sold, how long has production been going on? Also, what is considered an item? Is it a single tablet (the declaration appears to indicate that multiple tablets were given per treatment to subjects each day, and that this continued for months at a time) or is it a bottle comprising an entire therapeutic course? What is the relevance of any of this to the sales of other erectile dysfunction medicaments? In summary, it appears that the declaration of inventor Oleg I. Epshtein et al. fails to

establish the required nexus between alleged commercial success and the instant claimed product.

Further, it should be noted that a strong case of obviousness may be established such that the objective evidence of nonobviousness is not sufficient to outweigh the evidence of obviousness. See MPEP 716.01(d).

Newly presented claims 6 and 7 have been joined to the rejection of record. Independent claim 6 recites "monoclonal, polyclonal, or natural antibodies to a synthetic polypeptide corresponding to a fragment 1185- 1205 of an amino acid sequence of an endothelial Type III nitric oxide synthase (NO synthase)". The independent claim does not recite that the antibodies bind a peptide consisting of SEQ ID NO:x, but instead is much broader in that the term "corresponding" is interpreted to be open sequence language that is equivalent to comprising. Thus the recited antibodies need only bind to an antigen which comprises a sequence that "corresponds" to amino acids 1185-1205. Further, the indefinite article "a" rather than the definite article "the" is recited in the independent claim in reference to the peptide sequence. The use of the indefinite article indicates that the breadth of the claim is broader still in that the target antigen does not need to comprise the entirety of amino acids 1185-1205 but rather comprises truncations of this sequence, the smallest of which need only be two amino acids in length. Further, numerous NO synthases are known in the art, and the instant claim language does not limit the antibodies to binding any particular allelic sequence from any particular organism. Salerno et al. disclose antibodies that bind eNOS, and their eNOs antigens comprise sequences which "correspond" to amino acids 1185-1205. Therefore, the rejection of record meets the limitations of newly presented claims 6 and 7.

7. The following are new grounds of rejection necessitated by applicant's claim amendments received January 9, 2008.

8. Claims 1, 2, and 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, and 5 first recite "potentiated antibodies to NO synthase" and then proceed to recite that the potentiated antibodies do not bind NO synthase. Antibodies are typically characterized by their antigen specificity since the biological role of antibodies *in vivo* is binding antigens (Janeway et al, see entire selection). As such it does not appear logical that an artisan can have an antibody to an antigen when the antibody does not bind said antigen. What, if anything, does the antibody in the claimed medicaments bind? Thus the metes and bounds of the claimed invention are unknown.

Claims 6 and 7 are indefinite in that they recite "a polypeptide corresponding to a fragment of 1185-1205 of an amino acid sequence of an endothelial type II nitric oxide synthase". There are numerous NO synthases from numerous organisms known in the prior art, and reciting a fragment by it position within a larger amino acid sequence without explicitly identifying the exact sequence used renders the metes and bounds of the claim uncertain because different peptides will be made depending upon what is chosen as the reference sequence to establish the numbering convention. Indeed, Marsden et al. (of record on the 3/18/08 IDS) disclose NO synthases that differ in their length and sequence in Figure 1. Amending the claim to recite the recited fragment by SEQ ID number would be the most satisfactory way of obviating this rejection.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 2, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Davenas et al. (Nature 1988, 333:816-818, of record).

Davenas et al. disclose very low concentrations (dilution range of $1x10^{2}$ to $1x10^{120}$) of antibodies produced by repeated serial dilutions and exposure to the external factor of shaking by using a vortex (see entire document, particularly the abstract, page 816, and the legend of Fig. 1). Note that shaking/vortexing is a potentiation method as evidenced by the 6th paragraph of page 2 of the instant specification.

It is noted that the antibodies of Davenas et al. are disclosed as binding IgE. The antibodies of the instant invention are recited as not binding NO synthase. Antibodies that bind IgE do not bind NO synthase, and thus they meet that claim limitation. Further, the recitation of "effective in treating an erectile dysfunction" provides for an intended use of the claimed product. Intended use limitations do not provide patentable distinctiveness unless the intended use limitation is such that it alters the structure of the claimed compound in a demonstrable manner. See also MPEP 2111.02. In the instant case the product being claimed comprises a dilute composition comprising an antibody that does not bind NO synthase. Davenas et al. disclose such compositions.

Therefore, the prior art anticipates the claimed invention.

11. Claims 1, 2, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Epshtein et al. (Bulletin of Experimental Biology and Medicine, 1999, 3:286-289, of record).

Epshtein et al. disclose potentiated antiserum that has been diluted multiple times, the highest dilution being $1:10^{12}$. The potentiated antibodies were made by dilution and shaking (see particularly the right column of page 287).

It is noted that the antibodies of Epshtein et al. are disclosed as binding brain protein S100. The antibodies of the instant invention are recited as not binding NO synthase. Antibodies that bind S100 do not bind NO synthase, and thus they meet that claim limitation. Further, the recitation of "effective in treating an erectile dysfunction" provides for an intended use of the claimed product. Intended use limitations do not

provide patentable distinctiveness unless the intended use limitation is such that it alters the structure of the claimed compound in a demonstrable manner. See also MPEP 2111.02. In the instant case the product being claimed comprises a dilute composition comprising an antibody that does not bind NO synthase. Epshtein et al. disclose such compositions.

Therefore, the prior art anticipates the claimed invention.

Claim Objections

12. The term "amino acid' is misspelled in line 4 of claim 6. appropriate correction is required.

13. No claims are allowable.

14. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Primary Examiner
Art Unit 1644

/Michael Szperka/
Primary Examiner, Art Unit 1644